TBCI/BSC CSC

Correlative Science Workshop

Feb 23-24, 2009

TBCI/BSC CSC Workshop

- **Organizers**
  - Matt Ellis
  - Dan Hayes
  - Gabe Hortobagyi
  - Leah Kamin
  - Jean Lynn
  - JoAnne Zujewski
- **Ad Hoc Speakers**
  - Bob Becker — FDA
  - Mitch Dowsett — Royal Marsden
  - Lisa McShane — NCI
  - Torsten Nielson — BCAAC
  - Rich Simon — NCI

Objectives

- To develop consistent strategies and planning for evaluation of clinical utility of tumor markers by breast cancer cooperative groups
  - *Monday AM*
- To review currently available technologies for high throughput assays for DNA, RNA, and/or protein abnormalities designed to identify new signatures for prognosis or prediction
  - *Monday PM*

Objectives

- To specifically address two separate markers as examples
  - Intrinsic subtype (basal, luminal A, B, etc) signatures as prognostic factors
  - Chemotherapy predictive signatures
  - *Tuesday AM and PM*
- To address current policies and procedures of the CSC that might be modified
  - *Tuesday PM*

Workshop Action Items

- Consensus Principles of Approval
  - Case Control (vs. classic cohort)
  - Exploratory vs. Definitive
    - Single marker/profile
    - Multi (100s-1000s)
- Process
  - Chair
  - Vice-chair (election)
  - Nominate other reviewers in your groups
    - Clinical scientists
    - Laboratory scientists
    - Statisticians

Principles of Tumor Marker Utility

- Introduction to Tumor Marker Research & Review of Current TBCI CSC Activities
  - Dan Hayes, MD — University of Michigan
- *Tumor Marker Trial Designs*
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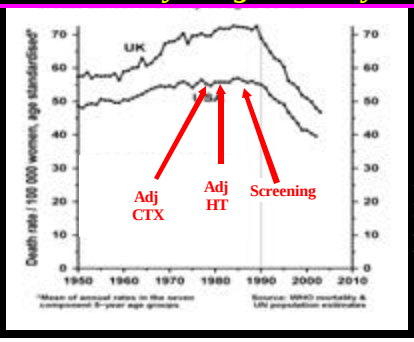
Recent decrease in UK and USA breast cancer mortality at ages 35-69 years



Modified from Peto et al. Lancet 355:1822, 2000

Adjuvant Systemic Therapy

- **Should All Patients Receive All Therapy?**
  - **If pt is willing to accept ANY toxicity for ANY benefit:** ***then treat her with everything***
  - **If pt is willing to forego SOME benefit to avoid SOME toxicity:** ***then select therapy carefully***
- **Depends on:**
  - **Well -defined subgroups that do or do not benefit from therapy**
  - **Patient's, Doctor's, and Society's Perspectives Regarding Risks, Benefits, and Costs of Therapy**

When is a Marker Clinically Useful?

- **It is either prognostic or predictive**
- **The magnitude of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable**
  - ***Greater chance for benefit***
  - ***Smaller toxicity risk***
- **The estimate of magnitude of effect is reliable**
  - ***Analytical reproducibilty***
  - ***Clinical trial/marker study design is appropriate***
  - ***Results are validated in subsequent well-designed studies (Levels of Evidence I or II)***

Henry N.L., Hayes DF; Oncologist. 11:541-52, 2006

Adjuvant Systemic Therapy

- **The goal of a prognostic or predictive tumor marker is to identify those patients who would FOREGO therapy to AVOID toxicities.**
  - **Some but not all "positive" patients will benefit**
  - **Few if any "negative" patients will benefit, but all are exposed to cost and toxicity**
- **How much absolute benefit will patients forego? Surprisingly small!**
  - ***Coates AS, New York, NY: John Wiley & Sons Ltd; 1992.***
  - ***Ravdin P, J Clin Oncol 1998;16:515-21.***
  - ***Lindley C, J Clin Oncol 1998;16:1380-87.***
- **AdjuvantOnline!**
  - ***Ravdin et al. J Clin Oncol 19:980-91, 2001***

ASCO Tumor Marker Guidelines Panel

ER, PgR	**Select Endocrine Therapy**
HER2	**Select Trastuzumab/Lapitinib**
UPA/PAI -1	**Avoid Chemo if ER+/Node neg**
Oncotype DX	**Avoid Chemo if ER+/Node neg**

Harris L., et al. J Clin Oncol. 2007

ASCO Tumor Marker Guidelines

- **Why Are the Guidelines So Conservative?**
  - Recommended only those markers for which results would change clinical decisions
  - Evidence-based
  - Lack of Level of Evidence I or II studies:
    - *A Tumor Marker Utility Grading Scale*

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

TMUGS: Levels of Evidence

Level	Definition
I	Prospective, Marker Primary Objective, Well-powered OR Meta-analysis
II	Prospective, Marker Secondary Objective
III	Retrospective, Outcomes, Multivariate Analysis
IV	Retrospective, Outcomes, Univariate
V	Retrospective, Correlation with Other Marker, No Outcomes

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MOST TUMOR MARKER STUDIES

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

Markers of Hormone Dependence & Sensitivity/Resistance to Endo Rx

ER

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  - *Assay is reproducible*
  - *Clinical trial/marker study design is appropriate*
  - *Results are validated in subsequent well-designed studies*

Estrogen Receptor as THE Predictive Factor for Endocrine Therapy

Compilation of Response Rates to several different ETs of >400 patients with METASTATIC Breast Cancer from several different countries:

Therapy	ER +	ER -
Ablative		
Ovariectomy	23/33 (69%)	4/53 (8%)
Adrenalectomy	32/66 (48%)	4/33 (12%)
Hypophysectomy	2/8 (25%)	0/8
Additive		
Estrogen	37/57 (65%)	5/58 (9%)
Androgen	12/26 (48%)	2/24 (8%)
Glucocorticoid	2/2 (100%)	—
Misc		
"Anti-estrogens"	8/20 (40%)	5/27 (21%)
"other"	2/3 (66%)	0/5
Total	*120/215 (56%)*	*23/208 (11%)*

Never published in Peer-Reviewed journal, that I can find!

McGuire W., et al. Estrogen Receptors in Human Breast Cancer. 1 -7, 1975

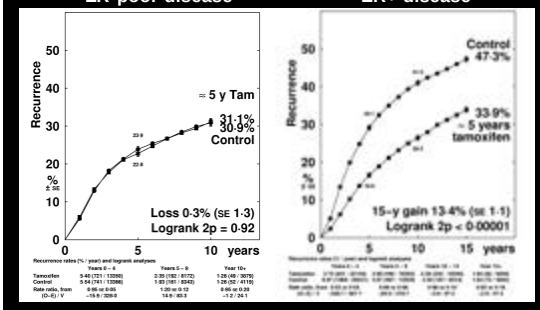
ER as THE Predictive Factor for Endocrine Therapy

- **McGuire data:**
  - **Based on ligand binding assay**
  - **Based on precious few patients-all with metastases**
  - **Based on multiple therapies**
- ***Level of Evidence III at best!***

- **BUT: of course we all believe them, and subsequent studies, especially Oxford Overview, confirm them**
  - **Level of Evidence I**

~5 years Tamoxifen vs not, split by ER status only: RECURRENCE

ER-poor disease **ER+ disease**



Early Breast Cancer Trialists' Collaborative Group. Lancet. 365:1687-717, 2005

Conclusions Regarding ER as Predictive Factor

- **ER negative (or "Poor") = No Benefit from endocrine therapy**
  - **With exception of PgR Positive (see below)**

- **ER + = Chance of benefit, but many ER positive patients (~ 30-50%) do not.**

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Tumor Markers

- **A bad tumor marker is as harmful as a bad drug!**
- **Would you use a drug if:**
  - **You aren't sure how it is mixed?**
  - **You aren't sure what the concentration is?**
  - **You don't have clinical data about how the drug might be useful?**
  - **You don't have reliable clinical research data to determine how much efficacy it might have?**

Tumor Markers: Carrots and Sticks

- **Research**
  - **Funding:** **NCI Cancer Biomarkers Study Section *(CBSS)***

    www.cms.csr.nih.gov
  - **Publication:** **Recommended Guidelines**
    - ***Mcshane et al, REporting Recommendations for Tumor MARker Prognostic Studies (REMARK)***
    - ***Bossuyt et al, Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative***
  - **Specimen Sources** **Breast Cancer Tissue Resource**

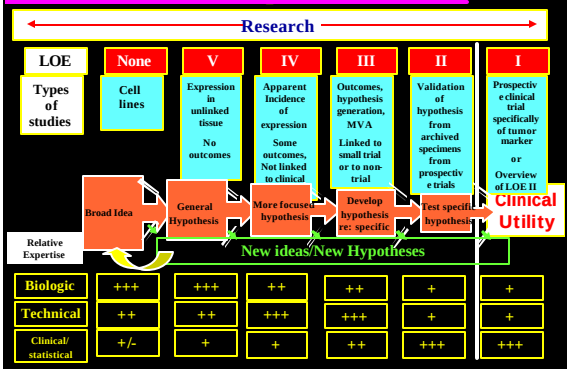
    Breast Cancer Inter-group Correlative Sciences Committee

    www.ctep.nih.gov/resources/tbci/correlative_studies.html

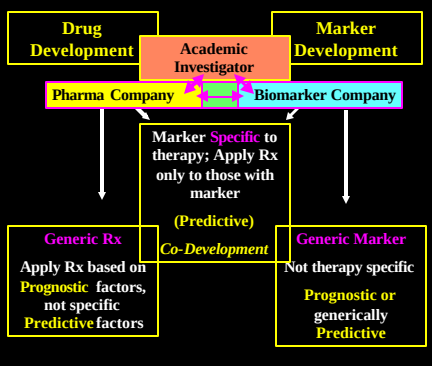
Tumor Markers: Carrots and Sticks

- **Clinical Use**
  - **Guidelines** — Evidence-based Guidelines Panels
    ASCO, NCCN, CAP, NACB
    www.asco.org
    www.nccn.org
  - **Regulatory/Reimbursement**
    - 3rd Party Tech Assessments
    - AACR/NCI/FDA
    - Center for Medical Technology Policy
    - Improved and Clear-cut FDA Rules
      - Center for Devices and Radiologic Health
      - *www.fda.gov/cdrh/guidance.html*

Tumor Marker Development/Flow Chart



Tumor Marker Development



Completed/Ongoing TBCI CSC Studies

Level	Definition	
I	Prospective, Marker Primary Objective, Well-powered OR Meta-analysis	
S0500	CTCs at first f/u to direct MBC chemotherapy	
TailorRx	21 gene RS in ER +/Node neg BC	
II	Prospective, Marker Secondary Objective	
C9344	HER2 (and ER) to predict paclitaxel	*Hayes NEJM '07*
E2100	VEGF/KDR SNPs and bevacizumab	*Schneider JCO '08*
S8814	21 gene RS in ER+/Node Pos Postmenopaual BC	*Albain SABCS '07*
III Retrospective, Outcomes, Multivariate		Analysis
S9313	Adj pts Rx'd with AC	*Porter, JNCI, '06; Tubbs JCO in press; Rimm SABCS '08*
	CycE, P27 HER2, TopoII, AQUA HER2, ER	
E2197	21 gene and multiple other genes in patients treated with AC or AT	*Goldstein JCO '08*
S8897	MPO SNPs in low risk/No Rx and in high risk Rx'd with CMF/CAF & tam	*Ambrosone SABCS '06*

Currently Approved TBCI Studies

Clinical trial	Markers/ methodology approved	Correlative study P.I.
NCIC-JMA17	Two gene expression signatures; AQUA multiple markers Novel gene expression profile development	Paul Goss, M.D., Ph.D., and Dennis Sgroi, M.D.
CALGB-9344 C9741	Extraction, amplification, and preservation of RNA from FFPE tissue	Matthew Ellis, M.B., Ph.D.
E2100	512-DASL gene set	Brian Leyland-Jones, MD, PhD
E2197	512 DASL gene set	Brian Leyland-Jones, MD, PhD
N9831	MYC, IGF-1R, PTEN, TOP2A	Edith Perez, MD (Monica REinhoz PhD, Robert Jenkins, MD)
S0221	SNPs in multiple genes: MPO, eNOS , MnSOD, GPX1, CAT, GSTP1, GSTAI, GSTM1, GSTT1, NQO1, NRF2	Christine Ambrosone PhD
NCIC MA27	GWAS	James Ingle, MD (RIKEN institute)
S9313	ALDH1 by IHC	Daniel F. Hayes, MD (Max Wicha, MD)

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Mitchell Dowsett Receives 2007 William L. Mcguire Award Recipient For Excellence In Breast Cancer Research

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Presenters Monday Afternoon

Almac	**Richard Kennedy**
Roche	**Walter Koch, Ph.D.**
Agilent	**Condie Carmack**
Illumina	**Gary Schroth**
Nanostring	**Gary Geiss**
GHI	**Steve Shak**